Cannabis Sensitivity Marks Genetic Psychosis Risk

BY JEFFREY S. EISENBERG

FROM ARCHIVES OF GENERAL PSYCHIATRY

Genetic risk for psychotic disorder might be expressed in part as sensitivity to the psychotomimetic effect of cannabis. And, cannabis use, combined with this preexisting risk, might cause positive and negative symptoms of psychosis, according to new research published online.

Studies have suggested that exposure to delta-9-tetrahydrocannabinol, the main psychotropic component of *Cannabis sativa*, induces psychotic symptoms in a substantial proportion of healthy controls. Also, prospective epidemiologic studies indicate that cannabis use not only predicts onset of psychotic disorder but also is linked with subthreshold expression of psychosis in the form of schizotypy or subclinical psychotic experiences.

Data for this study come from Genetic Risk and Outcome in Psychosis (GROUP), an ongoing longitudinal study in selected areas of the Netherlands and Belgium (Arch. Gen. Psychiatry 2010 Oct. 4 [doi:10.1001/archgenpsychiatry.2010.132]). The GROUP sample consists of 1,120 patients with nonaffective psychotic disorder, 1,057 siblings of these patients, 919 parents of patients and their siblings, and 590 unrelated controls.

Researchers used urinalysis to measure current substance abuse, sections of the Composite International Diagnostic Interview to assess long-term substance abuse, and an interview-based measure of schizotypy for the sibling–healthy control comparison. They performed sibling-control and cross-sibling comparisons using samples of patients with a psychotic disorder and community controls.

The main outcome measures were positive and negative schizotypy using the Structured Interview for Schizotypy–Revised for siblings and controls and self-reported positive and negative psychotic experiences using the Community Assessment of Psychic Experiences (CAPE) for siblings and patients. Patients and their siblings more often used cannabis than did control subjects, and more often were male and nonwhite, the researchers found. Additional results showed that:

- Siblings of patients displayed more than 15 times greater sensitivity to positive schizotypy associated with particularly current cannabis use by urinalysis, and a similar difference in sensitivity to its effect on negative schizotypy.
- Siblings exposed to cannabis resembled their patient relative nearly 10 times more closely in the positive psychotic dimension of CAPE vs. nonexposed siblings.
- No significant effect was apparent for the negative domain of CAPE, although the association was directionally similar (two times more resemblance; *P* interaction = .17).
- Cross-sibling, cross-trait analyses suggested that the mechanism underlying these findings was moderation (familial risk increasing sensitivity to cannabis) rather than mediation (familial risk increasing use of cannabis).

"An important issue revealed by this study is that while the relative effect sizes of differential sensitivity were high, absolute effect sizes, for example, of cannabis on schizotypy in unaffected siblings, were small," the researchers wrote. "It therefore follows that any study examining differential sensitivity will require a very large sample to demonstrate differences in sensitivity for an environmental risk factor between groups." ■

VITALS

Major Finding: Familial liability to psychosis appears to be partly expressed as a tendency to develop psychotic experiences after cannabis use.

Data Source: Genetic Risk and Outcome in Psychosis (GROUP), an ongoing longitudinal study in the Netherlands and Belgium.

Disclosures: The authors had no financial disclosures. The infrastructure for the GROUP study received funding from the Geestkracht program of the Netherlands Organisation for Health Research and Development, and from numerous universities and mental health care organizations in the Netherlands and Belgium. The analyses were supported by unrestricted grants from Janssen-Cilag, Eli Lilly & Co., AstraZeneca, and Lundbeck.

Buprenorphine Implants Reduce Opioid Dependence

BY MARY ANN MOON

FROM JAMA

Buprenorphine implants helped approximately 40% of patients addicted to opioids markedly reduce their drug use for 6 months in a phase III study of this new method of delivery.

Also, two-thirds of the study subjects who received the implants completed 24 weeks of treatment without cravings or withdrawal symptoms compelling them to drop out, said Dr. Walter Ling of the UCLA Integrated Substance Abuse Programs, Los Angeles, and associates.

In comparison, studies of sublingual buprenorphine found a median adherence of only 40 days in clinical settings, and 6-month clinical trials report subject retention rates of 35%-38%, they noted.

The implantable formulation of buprenorphine was developed to address dependent patients' problems with adherence and "diversion," or using the drug for some purpose other than treatment, such as selling it. The implants deliver an initial pulse of buprenorphine followed by the release of a constant, low level for 6 months. This avoids the peaks and troughs in plasma levels that occur with other methods of delivery.

Dr. Ling and his colleagues performed their industry-sponsored phase III study at 18 community addiction treatment centers across the United States. In all, 108 subjects were randomly assigned to receive four buprenorphine implants and 55 to receive four placebo implants in the subdermal space in the inner side of the nondominant arm.

The study subjects were allowed to receive supplemental sublingual buprenorphine-plus-naloxone tablets if they experienced significant withdrawal symptoms or cravings. They also were allowed to get one additional implant if necessary. All received individual drug counseling twice a week for 3 months and weekly thereafter.

The patients' use of illicit drugs was monitored throughout the study by urinalyses done 3 times per week.

The primary outcome measure was early treatment response, assessed as the percentage of the 48 urine samples from the first 16 weeks of the trial that were negative for illicit opioids. This rate was 40% with the buprenorphine implants, vs. 28% with the placebo implants (JAMA 2010;304:1576-83).

For the full 6-month treatment period, in which 72 urine samples were analyzed for each subject, 37% were negative for illicit opioids in the buprenorphine group, vs. 22% in the placebo group.

Adherence was significantly better with the active treatment at 16 weeks (82% with buprenorphine vs. 51% with placebo) and at the conclusion of the study (66% vs. 31%). Throughout the study, the implant group also had significantly lower scores on measures of opiate withdrawal and opioid craving.

No patients with buprenorphine implants were classified as treatment failures; 31% with placebo implants were.

Adverse reactions at the treatment site were common and expected in both groups, and resolved without incident in all but three patients. One serious adverse event may have been related to treatment: A pulmonary embolism and exacerbation of chronic obstructive pulmonary disease occurred in a patient with a history of pulmonary embolism and COPD, whose respiratory function might have been impaired by the buprenorphine. One patient in the placebo group also had a serious adverse event, cellulitis at the implant site.

"There were no clinically meaningful changes" in vital signs, physical exam findings, electrocardiograms, hematology values, or coagulation values.

There was no evidence of attempted removal of the implants, so "diversion" appears unlikely with this method of delivery, Dr. Ling and his associates said.

They cited among study limitations the fact that all patients received psychosocial counseling, and that the trial is not "statistically powered to examine efficacy within subgroups of patients." ■

VITALS

Major Finding: Among patients addicted to opioids, 40% were able to discontinue illicit drug use for 4 months and 37% for 6 months after receiving buprenorphine implants, while only 28% and 22%, respectively, discontinued illicit drug use after receiving placebo implants.

Data Source: A phase III, randomized placebo-controlled trial involving 163 patients treated at 18 U.S. clinical centers and followed for 6 months.

Disclosures: This study was funded by Titan Pharmaceuticals, maker of the buprenorphine implants, which was involved in the design and management of the study, data collection and analysis, and preparation and approval of the manuscript. Dr. Ling and his associates reported numerous ties to drug and device manufacturers.

VIEW ON THE NEWS

'Promising' New Delivery Method

These findings suggest that a promising new approach to opioid addiction may be close at hand. If further study shows that buprenorphine implants are as good as or better than current treatments, this study would represent a major advance, said Dr. Patrick G. O'Connor.

However, further improvement in the implant delivery system appears to be warranted, given the low plasma levels of buprenorphine that the study subjects attained and the degree to which they required supplemental sublingual drug.

In addition, the treatment is complex and resource intense, requiring implantation and removal procedures as well as specialized counseling. This study tested its use in special treatment centers with close medical supervision, but provided "relatively little information about how implants might be used in office practice," he said.

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